The Importance of Mortality Risk Assessment: Validation of the Pediatric Index of Mortality 3 Score

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Objective: To evaluate the performance of the newest version of the Pediatric Index of Mortality 3 score and compare it with the Pediatric Index of Mortality 2 in a multicenter national cohort of children admitted to PICU.

Design: Retrospective, prospective cohort study.

Setting: Seventeen Italian PICUs.

Patients: All children 0 to 15 years old admitted in PICU from January 2010 to October 2014.

Interventions: None.

Measurement and Main Results: Eleven thousand one hundred nine children were enrolled in the study. The mean Pediatric Index of Mortality 2 and 3 values of 4.9 and 3.9, respectively, differed significantly ($p < 0.05$). Overall mortality rate was 3.9%, and the standardized mortality ratio was 0.80 for Pediatric Index of Mortality 2 and 0.98 for Pediatric Index of Mortality 3 ($p < 0.05$). The area under the curve of the receiver operating characteristic curves was similar for Pediatric Index of Mortality 2 and Pediatric Index of Mortality 3. The Hosmer-Lemeshow test was not significant for Pediatric Index of Mortality 3 ($p = 0.21$) but was highly significant for Pediatric Index of Mortality 2 ($p < 0.001$), which overestimated death mainly in high-risk categories.

Conclusions: Mortality indices require validation in each country where it is used. The new Pediatric Index of Mortality 3 score performed well in an Italian population. Both calibration and discrimination were appropriate, and the score more accurately predicted

the mortality risk than Pediatric Index of Mortality 2. (*Pediatr Crit Care Med* 2016; 17:251–256)

Key Words: children; risk of mortality; outcome/quality measure; pediatric intensive care unit; standardized mortality ratio; validation studies

To assure the effective use of PICU resources, mortality prediction models are necessary to adjust for case mix variation and severity of illness by assessing the standardized mortality ratio (SMR). It is extremely important that risk of mortality indices is updated with predictors, coefficients, and models that are constantly recalibrated (1). The Pediatric Index of Mortality (PIM) is the only available score for the pediatric age group, which has been recently updated. The third edition (PIM 3) was published (2) in 2013, and it aimed to avoid a drift in calibration observed in previous data from two large national registries: the Paediatric Intensive Care Audit Network in the United Kingdom and the Ireland, Australian and New Zealand Paediatric Intensive Care registry (3, 4). Both reported an overprediction risk of mortality with poor performance in low-risk patients. In Italy, the previous version of PIM (5) was validated by a multicenter national study and showed good calibration and discrimination (6), but the observed mortality rate was lower than predicted. As suggested by the authors of the PIM score, new models should be validated in different settings and different populations to improve its general acceptance. The aim of this study was to evaluate the performance of the new risk of mortality model (PIM 3) and to compare it with the PIM 2 in an Italian PICU setting.

MATERIALS AND METHODS

Following the experience of other national registries (7–9), an Italian permanent registry for all PICU admissions was established in 2010 (http://www.tipnet.cineca.it). All Italian medical/surgical PICUs were invited to participate in Network delle Terapie Intensive Pediatriche (TIPNet). From 2010 to 2014, the number of units participating in the registry increased from 13 to 17 of 23 PICUs (56.5% and 73.9%, respectively) distributed throughout the country. Data collected included gender, age, reason for admission, Pediatric Overall Performance Category scale (10), comorbidities, type of admission, source of admission, risk of mortality on admission, PICU length of stay, and outcome. The PIM 2 was used from January 2010 to December 2013 and both PIM 2 and 3 from January to October 2014. The registry has been changed as needed to estimate the risk of death for both versions of the score. Furthermore, after assessing data consistency in the registry for the variables of interest for the years 2010–2013, the PIM 3 was retrospectively calculated applying the new risk diagnosis classification and the new coefficient for each variable. To verify appropriate data collection, the intraclass correlation coefficient was calculated among centers.

All consecutive admissions from January 2010 to October 2014 of children less than 16 years were considered for the study. Premature infants less than 36 weeks of gestational age were excluded from the analysis. Patients were excluded from the analysis if the data entry was incomplete.

STATISTICAL ANALYSIS

A descriptive analysis was made for the overall cohort and for each study year to verify homogeneity over time. Performance was validated by the SMR, which is the ratio of observed to expected (PIM predicted) deaths in a population with 95% CIs. CIs were estimated with the Byar approximation (11). Expected number of deaths was calculated as the average of overall predicted mortality times the number of patients in the population. Overall prediction of observed mortality was considered accurate when the SMR for the entire population was not significantly below or above 1. PIM 3 performance was tested with discrimination and calibration analysis and compared with PIM 2. Discrimination was assessed through the area under the receiver operating characteristic (ROC) curve (AUC) (12). Calibration was assessed by the Hosmer-Lemeshow (HL) goodness-of-fit test for deciles of risk (13). For analysis, patients were divided into age groups (newborn, infant, preschool, school, and adolescent), deciles of risk of death, study years, patient types (medical, surgical, and trauma), main reason of admission. Comparisons between PIM 2 and PIM 3 were made with the Mann-Whitney *U* test for comparing the risk of death and through the SMRs and AUC ROC analysis in the different groups of patients. We did sensitivity analyses, testing the PIM scores in a restricted dataset. A subpopulation of the overall cohort was selected by identifying and excluding two specific groups of children with a possible bias in the PIM determination: medical elective admissions from home and children transferred from another ICU. Finally, observed and expected deaths for each unit were plotted to identify units with unexpectedly low or high mortality.

Statistical analysis and data management were performed with Excel (Excel 2010; Microsoft, Redmond, WA), R (R Project for Statistical Computing version 3.1.3, Vienna, Austria) and NCSS (NCSS 9.0, NCSS, LLC, Kaysville, UT). Results were considered significant at p value of less than 0.05.

Children's Hospital Vittore Buzzi was the coordinator of the registry. The Ethical Committee performed the primary review and approved the study. Subsequently, each center participating in the registry received the approval from its ethical committee.

RESULTS

Of the 14,261 admissions in the registry at the time of the analysis, 1,098 (7.7%) were excluded because of incomplete data, whereas 2,054 (14.4%) were excluded due to age limits (**Fig. 1**). Therefore, 11,109 admissions (77.9%) were considered for the study.

The characteristics of children admitted were homogeneous among the four study years (**Table 1**). The majority of children were Caucasian (84.3%). Nine hundred eight children were admitted more than once (number of admissions range, 1–14) accounting for 1,629 admissions: 763 (46.8%) were planned admissions, 866 (53.2%) were unplanned. Ten admissions were unplanned within 48 hours from PICU discharge.

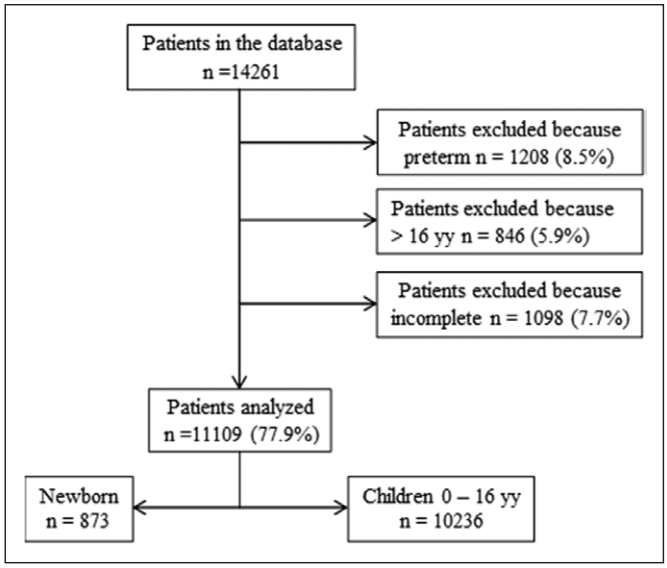

Figure 1. Flow chart of the study population.

Overall mortality was 3.9%, and mortality rate decreased from 5.4% in 2010 to 3.8% in 2014.

To calculate the PIM 3 score, 1,047 children were recoded following the new score rules. Six hundred forty-nine children (5.8%) with seizures were reallocated to the low-risk diagnosis group. Three hundred eighty-nine children (3.5%) who had a high-risk diagnoses in the PIM 2 score were recoded as very high risk for the PIM 3. The intraclass correlation coefficient was 0.974 (95% CI, 0.93–0.995) for both PIM 2 and 3, suggesting good agreement among raters.

PIM 3 Performance

The overall SMR was 0.98 (95% CI, 0.89–1.08). The AUC of the ROC curve for the entire cohort was 0.88 (95% CI, 0.86–0.89) (**Fig. 2*A***). Calibration described by the HL test through stratifications for deciles of risk was not significant ($p = 0.21$) (**Table 2**). Analysis in each strata showed a nonsignificant difference except in the lowest risk group, where observed deaths were significantly higher than expected (4 vs 1.25; $p < 0.05$). We removed planned admissions from home ($n = 301$) and those children admitted from another ICU ($n = 586$). Remaining 10,222 children showed an SMR of 1.01. Both tests were then applied in the selected population with an equal discrimination (AUC = 0.88) but a significant HL test ($p = 0.03$) (Table 2).

Comparison of PIM 2 Versus PIM 3

The mean PIM 2 risk of death was always significantly higher than the mean PIM 3 for the entire cohort (4.9 vs 3.9; $p < 0.05$) and in all subgroups analyzed with the exception of the trauma and adolescent groups and of 2010 and 2011 cohorts.

The overall SMR was 0.80 with PIM 2 score and 0.98 with PIM 3 score ($p < 0.05$). Discrimination estimated through the AUC for PIM 2 was 0.88 (95% CI, 0.86–0.89) not significantly different from the PIM 3 value ($p = 0.36$) (**Fig. 2*B***). The HL test was statistically significant for PIM 2 score ($p < 0.05$) (Table 2). Overprediction of deaths was observed in the highest risk deciles

TABLE 1. Characteristics of the Study Population

Variable	*n* = 11,109
Gender (women/men)	0.75
Study year	
2010	1,246 (11.2)
2011	2,638 (23.7)
2012	3,034 (27.3)
2013	2,270 (20.4)
2014	1,921 (17.3)
Age (mo)	
Mean (± SD)	46.3 (± 54.8)
Median (IQR)	20.6 (3.7–73.3)
Class of age	
Newborn (0–7 d)	873 (7.9)
Infant (0–12 mo)	3,758 (33.8)
Preschool (1–6 yr)	3,690 (33.2)
School (6–12 yr)	2,030 (18.3)
Adolescent (12–16 yr)	758 (6.8)
Chronic complex condition[a]	4,494 (43.9)
Admission unplanned[a]	6,160 (60.2)
Type of admission	
Medical	6,070 (54.6)
Surgical	4,459 (40.1)
Trauma	580 (5.2)
Length of stay	
Mean (± SD)	6.1 (± 15.5)
Median (IQR)	2 (1–6)
Mortality	432 (3.9)
PIM2	
Mean (± SD)	4.9 (± 11.9)
Median (IQR)	1.14 (0.4–3.8)
Expected mortality (E)	540.4
SMR (O/E)	0.80
PIM3	
Mean (± SD)	3.9 (± 10.8)
Median (IQR)	1.03 (0.3–3.2)
Expected mortality (E)	439.9
SMR (O/E)	0.98

IQR = interquartile range, PIM = Pediatric Index of Mortality, E = expected, SMR = standardized mortality ratio, O = observed.

[a]Rate estimated over 10,237 children (newborn excluded).

Data are expressed as *n* (%) for discrete variable or otherwise indicated. Expected mortality has been calculated as the sum of all the PIM score.

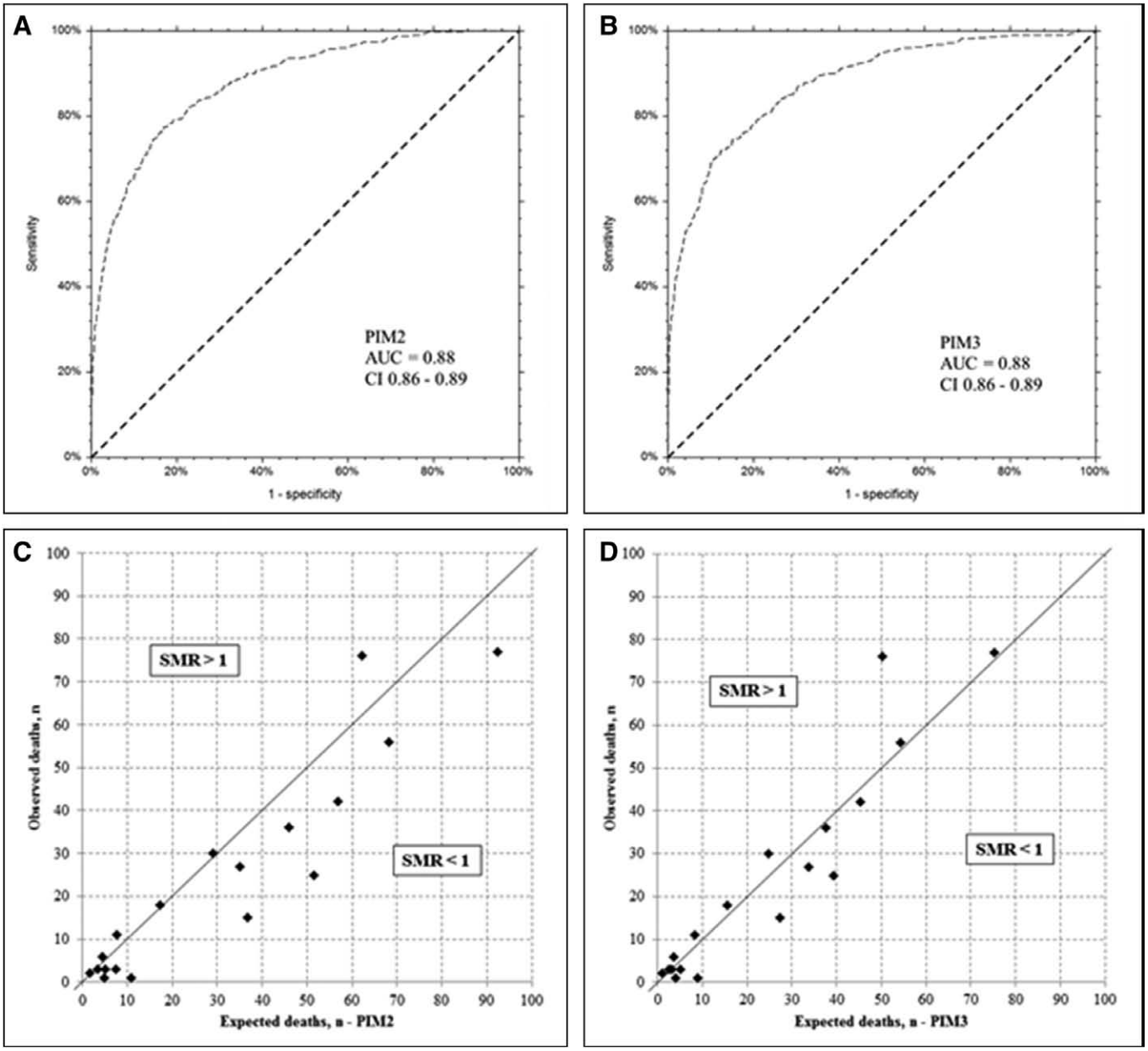

Figure 2. Comparison between Pediatric Index of Mortality (PIM) 2 and PIM3. **A** and **B**, Receiver operating characteristic curves. **C** and **D**, Predicted or observed deaths for each center. **A** and **B**, *Dotted line* is the reference line. **C** and **D**, *Continuous line* is the reference line for equal observed and expected deaths (standardized mortality ratio [SMR] = 1). AUC = area under the curve.

of PIM 2. PIM 3 performed better in most of the deciles except in the lowest risk group with an HL test that was not significant.

Expected versus observed deaths were plotted for each PICU using the two versions of the score. With the PIM 2, seven units had the observed mortality higher than the expected (SMR > 1) (**Fig. 2*C***), whereas with the PIM 3, nine units had an observed mortality higher than the expected (**Fig. 2*D***). Nevertheless, SMRs calculated using PIM 3 are closer to 1 (graphically shown by the dotted reference line) than using PIM 2.

Subgroup Performance

Calibration and discrimination were then assessed in all the subgroups. The numbers of expected deaths estimated by PIM 3 were not significantly different from those observed, whereas expected deaths predicted by PIM 2 were greater. PIM 3 performed better than PIM 2 in most of the categories considered apart from adolescents where the SMR was 1.4 versus 1.2, respiratory (1.15 vs 0.91) and cardiac surgical (1.2 vs 0.69). The AUC of the ROC curves was similar for both the scores and always greater than or equal to 0.80 in all groups (AUC range, 0.80–0.93).

DISCUSSION

Mortality scores are developed in specific populations with varying characteristics of case-mix, available resources, and treatment protocols, which may be different in other national settings. It is therefore important to have an external validation

TABLE 2. Hosmer-Lemeshow Test for Deciles of Risk

PIM2 Overall Cohort				PIM3 Overall Cohort				PIM3 Selected Cohort			
Values	*n*	O	E	Values	*n*	O	E	Values	*n*	O	E
0.0002–0.0017	1,314	0	1.46	0.0001–0.0018	1,231	4	1.25	0.0001–0.0017	1,073	4	0.99
0.0017–0.0032	921	1	2.15	0.0018–0.0025	1,047	1	2.09	0.0017–0.0023	1,029	0	1.96
0.0032–0.0057	1,112	8	4.86	0.0025–0.0043	1,074	3	3.62	0.0023–0.0042	988	3	3.04
0.0057–0.0084	1,134	8	7.97	0.0043–0.0064	1,112	8	5.73	0.0042–0.0058	1,038	8	5.01
0.0084–0.0115	1,079	11	10.69	0.0064–0.0104	1,095	11	8.89	0.0058–0.0095	985	7	7.34
0.0115–0.0171	1,111	15	15.59	0.0104–0.0151	1,168	16	15.14	0.0095–0.0142	1,025	19	12.42
0.0171–0.0283	1,111	24	24.72	0.0151–0.0243	1,052	23	20.20	0.0142–0.0221	1,022	20	17.74
0.0283–0.0495	1,111	30	42.43	0.0243–0.0409	1,115	38	36.26	0.0221–0.0389	1,044	33	31.91
0.0495–0.1023	1,106	70	77.35	0.0409–0.0801	1,105	63	61.36	0.0389–0.0756	996	52	52.69
0.1023–0.9981	1,110	265	353.33	0.0801–0.9985	1,110	265	285.62	0.0756–0.9985	1,022	240	249.57
	11,109	432	540.55		11,109	432	440.16		10,222	386	382.67
	$p < 0.001$				$p = 0.21$				$p = 0.03$		

PIM = Pediatric Index of Mortality, O = observed deaths, E = expected deaths.
Deciles of risk were derived by the Hosmer-Lemeshow function of R statistical software. Pediatric Index of Mortality values are reported as decimal.

to assess the model in each country using it. This study represents the first assessment of the new version (PIM 3) published in 2013 (5) in a different setting than the one in which it was developed.

Our results showed that using PIM 3, the SMR for the entire population was 0.98. The score performed very well in discrimination and in calibration in our population. Discrimination was good with an acceptable AUC for the entire cohort. The observed value of 0.88 is the same as described by the original article. Furthermore, discrimination was good among each subgroup analyzed. Classification for year of study, age, and admission diagnosis revealed an AUC always higher than 0.80. Calibration along deciles of risk through the HL test was not significant. Besides the statistical importance of this result, as clearly explained by Shann (14), the HL test should be evaluated in depth in each of the 10 rows. Seven of 10 strata had an SMR higher than one, but most had a small difference between observed and expected deaths and above all without clinical meaning. The major difference was observed in the lowest risk of death decile. All four deaths recorded were children with chronic complex conditions (chronic renal failure, postanoxic cerebral palsy, epilepsy, and congenital malformation). Two of these children had severe disability on PICU admission, and life-sustaining therapies were withdrawn in agreement with the parents due to the poor quality of life expectancy. Both these patients did not have a high or a very high-risk diagnosis and account for a low risk of mortality score when compared with their general condition.

The new score was developed to improve mortality prediction when compared with PIM 2, which had a tendency to over predict deaths. PIM 3 appears to perform better than PIM 2. Its SMR was significantly more appropriate than PIM 2 with almost 100 less predicted deaths. In the previous study conducted in Italy to validate the PIM score, overprediction of death had been observed for PIM 2 (6).

Although the PIM score is a general mortality score, a criticism may arise for the prediction risk of death among newborns. Indeed, in this group, both the PIM 2 and 3 versions overpredicted deaths with a poor SMR. A possible reason is the risk of death associated with given systolic blood pressure. As already discussed by Marcin and Wetzel (15), the PIM score has a possible limitation in the "one-size-fits-all" objective. Indeed, the ideal systolic blood pressure associated with the lowest risk of death is 120 mm Hg, and all the pressures lower than this value increase the risk of death. It is obvious that newborns, who have a physiologically lower pressure, would have a spurious PIM score.

The choice to exclude children with planned admission from home and children admitted from another ICU was justified by possible confounding factors in these two categories. The first group has a low potential risk of dying because they come into the hospital to set or adjust long-term home mechanical ventilation. The second group includes children who had arrived from another ICU and who had already received intensive care treatment. Therefore, we believe that the score does not accurately reflect the primary patient condition. Admission from another common ward is a different matter. Most of the time, these patients are not yet stabilized, either for respiratory or for cardiovascular problems, and are transferred due to the inability of the hospital of origin to treat critically ill children. The removal of these patients changed slightly the score validation, for SMR, calibration, and discrimination.

To date, there are no other published studies that have examined PIM 3 performance. The strength of this study is that we analyzed a cohort of more than 10,000 children admitted to 17 different PICUs. To date, only a few external validation studies

in pediatric intensive care have been performed with a sufficiently large sample size (6, 16–19). As discussed by Shann (20), a severity score should not be validated in a single unit or in a too small population because of possible inappropriate statistical results.

Our study has two major limitations. The first is that most of the analysis (from 2010 to 2013) has been undertaken in a retrospective manner. However, PIM 3 maintained most variables from the previous version. The major changes were those regarding the coefficient of each variable and the classification of the risk diagnosis. Our registry was developed with the aim to collect data for research purposes, and all the information required to calculate PIM scores had been stored. Nevertheless possible inaccuracy, mainly for new admission diagnoses such as necrotizing enterocolitis and seizures, might be possible (underestimation). The second limitation is that data were collected over 5 years, and outcomes might change over time. These changes should be detected by the score; indeed, mortality rate decreased from 2010 to 2014 and the score performed better in the more recent study years (2013–2014) than in the previous 3 years.

CONCLUSIONS

PIM 3 is an easy to use and valid instrument to assess mortality risk in a PICU population. Due to local differences in national health services that might influence performance, some authors have suggested that local adjustment of the coefficients used in severity of illness scores might enhance local performance. The use of local coefficients would, however, make comparison among PICUs in different countries problematic. In contrast to this, our results demonstrate that the standard PIM 3 score performed well in our Italian population. This is consistent with the use of a reliable international model for comparison among ICU populations in many countries.

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